Design and Synthesis of Novel Chiral Dendritic Species Derived from Bile Acids

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Bile acids have been used for the first time as the building block for the construction of dendritic units. Orthogonally functionalized 7-deoxycholic and cholic acid derivatives were synthesized. The construction of a bile acid heptamer, a nonamer, and a decamer using the convergent strategy are described in detail. Chromatographic, spectral, and optical properties of these molecules have been investigated. Molecular modeling suggests that these molecules have globular shapes with nanometric dimensions.

Background and Design

Ever since their first appearance in the literature,[1] the chemistry of dendrimers has grown enormously.[2] In recent years, there has been a shift in the direction of research from the synthetic aspects of macromolecular construction to functional dendritic species.[3] Dendrimer chemistry has been blended with several contemporary themes such as host−guest chemistry,[4] metalloorganic chemistry,[5] luminescent materials,[6] catalysis,[7] medicinal chemistry,[2d] and polymers.[8] Chiral dendritic species appeared in the chemical literature shortly after the first achiral version was reported.[9] These molecules received increased attention during the past decade due to their potential applications in enantioselective clathration, leading to applications in separation, catalysis, and sensor technology. Additionally, studies on the optical activity of chiral dendritic species have been of immense interest because of a search toward *chiral secondary structures.* As a dendrimer possesses three distinct regions, viz. the core, the branching units, and the end groups, the incorporation of chirality in these species can in general be achieved by choosing a chiral core or chiral branching units, by capping the end groups with a chiral moiety or by a combination of the aforementioned parameters. The findings of Newkome (capping the **end groups** with amino acids),[10] Seebach [using chiral tris(hydroxymethyl)methane derivatives as the **core**],[11] Chow (D- and L-tartaric acid derived **branching units**),[12] Meijer [amino acid terminated poly(propylene imine) dendrimers],[13] and McGrath (information that the conformation of the chiral dendrimers can be obtained using small molecules as model compounds)[14] led to a significant understanding on this subject.

Among the naturally available chiral species, amino acids,[15] nucleic acids,[16] sugars,[17] and tartaric acid[12] have already been exploited in dendritic chemistry. Bile acids (**1**−**3**, Chart 1), forming another class of chiral molecules, have been extensively used in many facets of chemistry[18]

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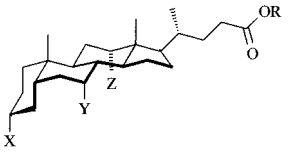
Chart 1

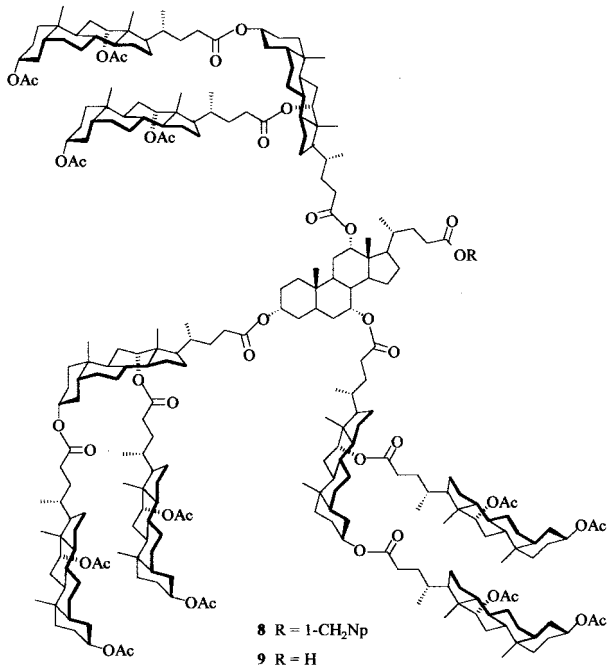


1 Lithocholic acid: X = OH, Y = Z = H
2 Deoxycholic acid: X = Z = OH, Y = H
3 Cholic acid: X = Y = Z = OH

such as asymmetric synthesis,[19] molecular recognition,[20] drug delivery systems,[21] and linear polymer chemistry,[22] and as cationic facial amphiphiles.[23] Several features of bile acids make them attractive chiral building blocks. The chemistry involved in constructing dendritic species from these genuine AB_2 (deoxycholic acid) and AB_3 (cholic acid) building blocks is straightforward, unlike with many other building blocks[24] in which functional group modifications are needed. These naturally occurring group of chiral amphifacial molecules are known to form helical aggregates.[25] Therefore, we felt that it would be quite interesting to examine the possible existence of helical conformations in bile acid derived dendritic structures. The bio-compatible nature of these chiral dendrons could also be exploited for other applications.[26] We recently communicated the synthesis of a heptamer and a nonamer derived from bile acid units.[27] In this paper, we disclose the full details of the work including the synthesis of a bile acid based decamer (Figure 1) and some properties of these molecules.

Results and Discussion

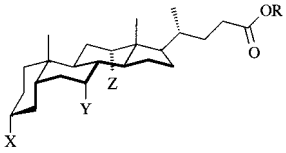
Synthesis. Of the two general methods available for the construction of dendrimers (the "*divergent strategy*" developed independently by Tomalia and Newkome[28] and the "*convergent strategy*"[29] of Fréchet), we chose the convergent method. Orthogonal protection of bile acids (**2** and **3**) with acetate and 1-naphthylmethyl groups[30] generated compounds **4**−**7** (Chart 2). All the esterification reactions were carried out by the Oppenauer protocol.[31] The carboxylic acid was converted to the corresponding acid chloride and reacted with the polyol in the presence



8 R = 1-CH_2Np
9 R = H

Figure 1. Bile acid decamer.

Chart 2



4 deoxycholic acid 3α, 12α-diacetate
X = Z = OAc, Y = H, R = H
5 1-naphthylmethyl deoxycholate
X = Z = OH, Y = H, R = 1-CH_2Np
6 cholic acid 3α, 7α, 12α-triacetate
X = Y = Z = OAc, R = H
7 1-naphthylmethyl cholate
X = Y = Z = OH, R = 1-CH_2Np

of CaH_2 and $PhCH_2Et_3N^+Cl^-$ in refluxing toluene. Trimer **10** was obtained from **4** and **5** in 67% yield and was deprotected by hydrogenolysis to yield trimer-COOH, **11**. Compound **11** on reaction with **5** generated heptamer **12** ($2 \times 3 + 1$) in 74% yield, which was deprotected to afford heptamer-COOH **13** (Scheme 1). The reaction between **11** and **7** also proceeded smoothly to generate the decamer ($3 \times 3 + 1$) **8** in 72% yield, which was subsequently converted to **9**. In an analogous manner, **6** and **7** afforded tetramer **14** which was converted to tetramer-COOH, **15**. Nonamer **16** ($2 \times 4 + 1$) was obtained upon the reaction of **15** with **5**, which subsequently afforded nonamer-COOH **17** (Scheme 2). All the dendrons were characterized by IR, ^1H and ^{13}C NMR, UV, MALDI-TOF MS,[32] and, wherever possible, HPLC and elemental analysis.

HPLC, UV, and NMR Analysis. The compounds containing the naphthylmethyl group were examined by reversed-phase HPLC, which provided information about their purity. The order of elution (increasing retention

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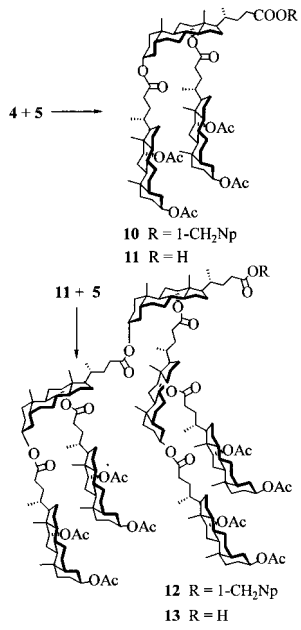
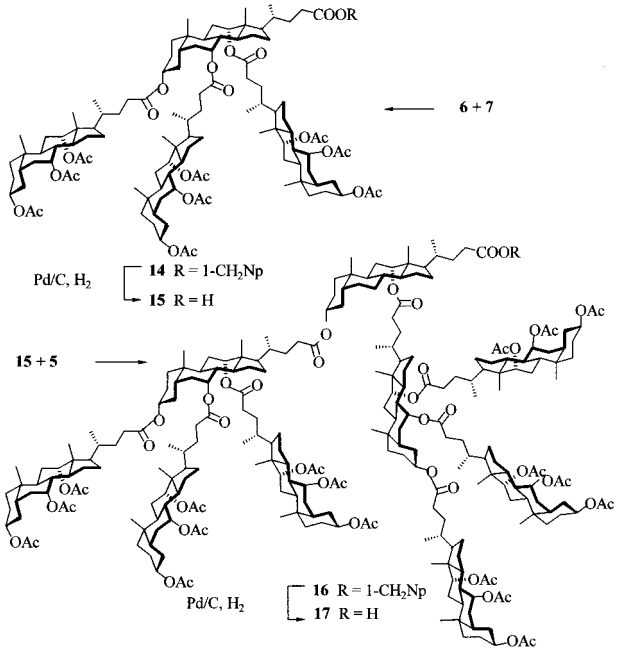
Scheme 1



Scheme 2



time) on a C-18 column was found to be **14** < **16** < **10**< **12** < **8**. Thin layer chromatographic analysis on silica gel did not show a directly reversed order: the R_f values increased in the order **16** < **14** < **8** < **12** < **10** (EtOAc/hexanes, 2:3 v/v).

The naphthylmethyl group served as a UV marker, and the quantitative UV spectral analysis of these dendrons gave an independent measurement of their approximate molecular weights, which were found to be in reasonable agreement (typically within ±10%) with the calculated molecular weights.

The methylene hydrogens of the naphthylmethyl group also served as a label in ^{1}H NMR of these compounds. In all the spectra the integration for the methylene unit was set to 2 and by comparison of other integrations information about the number of bile acid units present was obtained. The absence of signals in the 3−4 ppm region

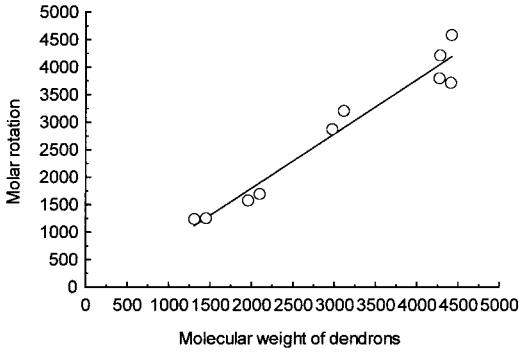


Figure 2. Plot of molar rotation vs molecular weight of dendrons.

suggested the absence of β hydrogens attached to unesterified OH groups.[33]

Chiroptical Properties. The molar specific rotation values (in chloroform) showed a roughly linear relationship with the number of bile acid units in each dendron (or its molecular weight, Figure 2), thereby suggesting the absence of any chiral conformation. This was also supported by the lack of CD in THF solutions of most of the dendrons, except decamers **8** and **9**, which showed a weak CD (data not shown). This suggests that higher oligomers (beyond the decamer) might show well-defined secondary structures.

Molecular Modeling. Insight II optimization (version 2.3.5, CVFF force field) of the dendrons was carried out to get information about their dimensions. Modeling shows that these molecules have dimensions of the order of 2.6−5.2 nm. The structures obtained by Insight II appear to be compact/globular. One of the possible conformations of the decamer skeleton is shown in Figure 3.

Conclusion

This work demonstrates the first utilization of large bile acid units in dendrimer chemistry. Because of the size of the building blocks, it is possible to achieve significant differential gain in dendron dimensions with additional repeating units. These molecules showed a linear relationship between molar specific rotation of dendrons and the number of bile acid units (or their molecular weights), in line with observations made by others. Compounds **9**, **11**, **13**, **15** and **17** provide a free carboxylic acid group which can easily be utilized for further transformation into bigger macromolecules. The design and synthesis of functional dendrimers from these dendrons is in progress in our laboratory, and will be reported in due course.

Experimental Section

General Remarks. Standard protocols were followed for the purification of solvents and reagents. For other details, see ref 19.

(33) Peaks arising out of the same type of β hydrogens generally coalesced into a single peak. In many cases we observed two sets of 3β and 12β hydrogens, in the ratio of 1:*n* for an (*n* + 1)-mer, whereas the 7β hydrogens were never split. The smaller peak (1 H) in the case of 12β was always shifted *upfield*, whereas for 3β hydrogens it shifted *both* upfield and downfield with respect to the more intense peak. The acetate signals also showed splitting. The ratio of 12 protons (from OAc) from the trimer showed that the signals were split in the ratio 3;3;6. Even with higher oligomers splitting was observed. The characteristic angular methyl region became too complex with higher oligomers and little information could be obtained.

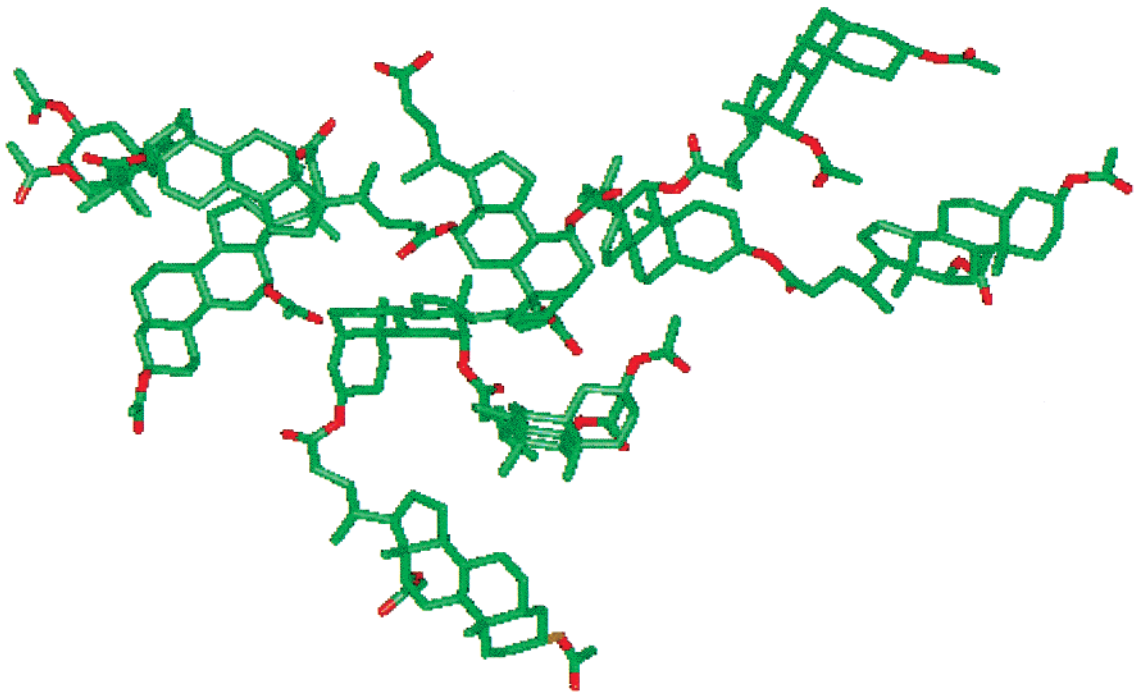


Figure 3. Representative structure of decamer **9**.

3α,12α-Diacetyloxy-5*β*-cholanic acid, 4. To an ice-cooled suspension of **2** (4.15 g, 10.57 mmol) in Ac_2O (23 mL, 243 mmol) were added Et_3N (23 mL, 166 mmol) and DMAP (4-(dimethylamino)pyridine, 0.080 g, 0.654 mmol) and the mixture stirred at room temperature for a period of 23 h. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (2 × 80 mL). The organic layer was washed with 1 M HCl (100 mL) and water (100 mL). The crude product obtained after evaporating the solvent was chromatographed on silica gel using 15−30% EtOAc/hexanes to yield 4.64 g (92% yield) of a white solid.

IR (film, cm^{-1}): 2940, 2860, 1730, 1700, 1460, 1450, 1380, 1360, 1240, 1190, 1150, 1030, 970, 750.

^1H NMR ($CDCl_3$, 300 MHz) δ: 5.09 (s, 1 H), 4.70 (s, 1 H), 2.36 (m, 1 H), 2.25 (m, 1 H), 2.11 (s, 3 H), 2.04 (s, 3 H), 1.84−0.98 (m), 0.91 (s, 3 H), 0.82 (d, 3 H, J = 6.3 Hz), 0.73 (s, 3 H).

3α,7α,12α-Triacetyloxy-5*β*-cholanic Acid, 6. In an analogous manner, **3** (2.64 g, 6.48 mmol) yielded 1.68 g of the title compound (48% yield).

IR (film, cm^{-1}): 2960, 2860, 1720, 1700, 1470, 1440, 1380, 1360, 1240, 1150, 1020, 950, 890, 750.

^1H NMR ($CDCl_3$, 300 MHz) δ: 5.09 (s, 1 H), 4.91 (s, 1 H), 4.58 (m, 1 H), 2.39 (m, 1 H), 2.27 (m, 1 H), 2.14 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.00−0.96 (m), 0.92 (s, 3 H), 0.83 (d, 3 H, J = 6.3 Hz), 0.74 (s, 3 H).

1-Naphthylmethyl 3α,12α-Dihydroxy-5*β*-cholan-24-oate, 5. To a solution of **2** (2.58 g, 6.58 mmol) in DMF (3 mL) were added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene,1.2 mL, 8.03 mmol) and 1-naphthylmethyl chloride (1.0 mL, 6.80 mmol), and the mixture was stirred at 55 °C for 24 h. The reaction mixture was poured in water (100 mL) and extracted with EtOAc (2 × 75 mL). The organic layer was washed with 150 mL each of water, 1 M HCl, water, and brine. The crude material obtained after removal of the solvent was column chromatographed on silica gel (18 × 1.6) using 40% EtOAc/$CHCl_3$ to yield 2.78 g (79%) of the title compound.

IR (film, cm^{-1}): 3400(b), 2940, 2880, 1740, 1450, 1380, 1180, 1050, 800, 760.

^1H NMR ($CDCl_3$, 300 MHz) δ: 8.02 (d, 1 H, J = 7.2 Hz), 7.90−7.84 (m, 2 H), 7.58−7.43 (m, 4 H), 5.58 (s, 2 H), 3.93 (s, 1 H), 3.61 (m, 1 H), 2.39 (m, 1 H), 2.27 (m, 1 H), 1.86−0.99 (m), 0.93 (d, 3 H, J = 8.4 Hz), 0.90 (s, 3 H), 0.60 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.10, 133.65, 131.56, 131.51, 129.16, 128.63, 127.41,126.45, 125.85, 125.19, 123.51, 72.99, 71.59, 64.33, 48.07, 47.14, 46.35, 41.98, 36.30, 35.90, 35.17, 35.03, 34.02, 33.47, 31.31, 30.82, 30.30, 28.50, 27.36, 27.06, 26.04, 23.58, 23.05, 17.12, 12.56.

UV (THF, 263 μM), λ(log ϵ)): 292.3 (3.71), 288.2 (3.70), 281.5 (3.88), 271.6 (3.80), 228.4 (4.01).

LRMS: 532 (<10%) (M^+).

1-Naphthylmethyl 3α,7α,12α-Trihydroxy-5*β*-cholan-24-oate, 7. In an analogous manner **3** (1.24 g, 3.03 mmol) yielded 1.23 g (77%) of a white solid.

IR (film, cm^{-1}): 3360 (b), 2920, 2860, 1720, 1510, 1450, 1370, 1300, 1220, 1160, 1080, 1040, 980, 950, 910, 860, 790, 750, 660.

^1H NMR ($CDCl_3$, 300 MHz) δ: 8.02 (d, 1 H, J = 8.1 Hz), 7.90−7.84 (m, 2 H), 7.59−7.43 (m, 4 H), 5.58 (s, 2 H), 3.93 (s, 1 H), 3.84 (s, 1 H), 3.45 (m, 1 H), 2.42 (m, 1 H), 2.30 (m, 1 H), 1.99−1.00 (m), 0.94 (d, 3 H, J = 6 Hz), 0.88 (s, 3 H), 0.61 (s, 3 H)

^{13}C NMR ($CDCl_3$, 22.5 MHz) δ: 173.97, 133.56, 131.39, 129.01, 128.47, 127.17, 126.30, 125.65, 125.00, 123.37, 72.77, 71.58, 68.12, 64.11, 46.77, 46.12, 41.35, 39.19, 34.96, 34.53, 31.17, 27.27, 26.08, 22.18, 17.08, 12.21.

UV (THF, 104 μM), λ(log ϵ)): 292.3 (3.73), 288.1 (3.73), 281.4 (3.90), 271.5 (3.82), 228.1 (4.26).

LRMS: 548 (<10%) (M^+).

Trimer (OAc, $COOCH_2Np$), 10. To a suspension/solution of **4** (0.752 g, 1.57 mmol) in toluene (4 mL) was added oxalyl chloride (0.7 mL), and the mixture was stirred in the presence of 10 μL of DMF for 25 min. Volatiles were removed under reduced pressure, and the residue was dried under vacuum for 35 min. To **5** (0.259 g, 0.486 mmol) dissolved in toluene (1.5 mL) were added CaH_2 (0.430 g, 10.2 mmol) and $BnNEt_3$-Cl (0.030 g, 0.132 mmol). To this suspension was added the acid chloride dissolved in toluene (4.5 mL), and the mixture was refluxed for 2 days. The reaction mixture was filtered through Celite, and volatiles were removed. To the residue dissolved in EtOAc (10 mL) were added Et_3N (0.3 mL) and water (0.3 mL), and the mixture was stirred for 1.5 h. This solution was diluted with EtOAc (60 mL) and washed with water (3 × 40 mL). The evaporation of the organic layer yielded the crude product which was chromatographed on silica gel (28 × 1.1) with 15% EtOAc/hexanes to yield 0.475 g (67%) of a white solid.

IR (film, cm^{-1}): 2920, 2860, 1720, 1440, 1370, 1240, 1150, 1080, 1020, 750.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.01 (d, 1 H, J = 7.8 Hz), 7.91−7.84 (m, 2 H), 7.56−7.43 (m, 4 H), 5.58 (s, 2 H), 5.08, 5.04 (s, s, 3 H), 4.70 (m, 3 H), 2.30−2.18 (m), 2.10, 2.09, 2.04 (singlets, OAc protons), 1.84−0.98 (m), 0.92−0.65 (m, angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.90, 173.54, 173.31, 170.53, 170.40, 170.32, 133.70, 131.52, 129.24, 128.69, 127.45, 126.50, 125.91, 125.25, 123.52, 75.86, 74.16, 64.40, 49.39, 47.83, 47.65, 45.01, 41.77, 35.64, 34.68, 34.36, 34.01, 32.23, 31.73, 31.52, 31.26, 30.89, 27.31, 26.87, 26.61, 25.86, 25.62, 23.41, 23.05, 21.44, 21.37, 17.49, 17.43, 12.49, 12.43. 12.31.

UV (THF, 81.4 μM), λ(log ϵ)): 292.3 (3.74), 281.5 (3.92), 271.7 (3.84), 228.0 (4.36).

HPLC: t_R = 17.1 min (15% THF/MeOH, λ = 280).

MALDI-TOF MS: 1474.2 (M + Na^+, 1473.0), 1490.2 (M + K^+, 1489.1).

Anal. Calcd for $C_{91}H_{132}O_{14}$: C, 75.37; H, 9.18. Found: C, 75.05; H, 9.38.

$[\alpha]^{25}_D$ (*c* 1.5, $CHCl_3$): 86.6.

Trimer (OAc, COOH), 11. To a solution of **10** (0.276 g, 0.190 mmol) in EtOAc (4 mL) under H_2 atmosphere was added 10% Pd/C (0.077 g, 0.0729 mmol), and the mixture was stirred under H_2 atmosphere for 42 h. The reaction mixture was filtered, and volatiles were removed under reduced pressure to yield the crude product which was chromatographed on silica gel (15 × 1.1) with 30−50% EtOAc/hexanes to yield 0.198 g (80%) of the title compound.

IR (film, cm^{-1}): 2920, 2860, 1730, 1440, 1370, 1240, 1160, 1020, 750.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.09 (s, 3 H), 4.70 (s, 3 H), 2.34−2.18 (m, 3 H), 2.11, 2.10, 2.04 (singlets, OAc protons), 1.84−0.95 (m), 0.91−0.73 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 179.00, 173.59, 173.34, 170.59, 170.44, 75.87, 74.29, 49.49, 47.84, 45.09, 45.01, 41.78, 35.66, 34.68, 34.51, 34.38, 34.02, 32.23, 31.74, 30.85, 27.36, 26.86, 26.61, 25.87, 25.63, 23.46, 23.05, 21.44, 21.38, 17.49, 12.53, 12.43.

MALDI-TOF MS: 1333.8 (M + Na^+ 1332.8), 1350.1 (M + K^+ 1348.9).

Anal. Calcd for $C_{80}H_{124}O_{14}$: C, 73.36; H, 9.54. Found: C, 73.88; H, 9.94.

$[\alpha]^{25}_D$ (*c* 0.38, $CHCl_3$): 94.7.

Heptamer (OAc, $COOCH_2$Np), 12. The procedure for the synthesis of **10** was followed. From **11** (0.223 g, 0.170 mmol) and **5** (0.033 g, 0.062 mmol) was obtained 0.142 g (74%) of the title compound (white solid).

IR (film, cm^{-1}): 3400 (b), 2940, 2880, 1730, 1450, 1370, 1240, 1170, 1090, 1020, 970, 750.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.01 (d, 1 H, J = 7.8 Hz), 7.90−7.84 (m, 2 H), 7.58−7.43 (m, 4 H), 5.58 (s, 2 H), 5.08 (s, 7 H), 4.70 (m, 7 H), 2.28 (m), 2.19 (m), 2.11, 2.09, 2.04 (singlets, OAc protons), 1.84−0.97 (m), 0.90−0.64 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.78, 173.50, 173.48, 173.38, 173.26, 173.17, 173.15, 170.46, 170.34, 170.25, 170.21, 133.65, 131.53, 131.46, 129.18, 128.64, 127.39, 126.43, 125.86, 125.18, 123.45, 77.20, 75.79, 75.75, 75.60, 75.54, 74.10, 74.07, 73.85, 64.33, 49.48, 49.33, 47.96, 47.90, 47.77, 47.70, 47.63, 45.06, 45.02, 44.98, 44.94, 41.72, 35.60, 34.70, 34.63, 34.56, 34.54, 34.46, 34.35, 34.31, 34.25, 33.95, 32.26, 32.18, 31.67, 31.48, 31.20, 30.99, 30.79, 27.31, 26.80, 26.55, 25.81, 25.55, 23.40, 23.00, 21.38, 21.31, 17.45, 17.40, 17.37, 12.47,12.44, 12.37, 12.26.

UV (THF, 74.1 μM), λ(log ϵ)): 292.3 (3.72), 281.5 (3.89), 271.7 (3.82), 228.0 (4.34).

HPLC: t_R = 14.5 min (30% THF/MeOH, λ = 280).

MALDI-TOF MS: 3143.0 (M + Na^+ 3139.4), 3159.4 (M + K^+ 3155.5).

Anal. Calcd for $C_{195}H_{292}O_{30}$: C, 75.15; H, 9.44. Found: C, 75.33; H, 9.83.

$[\alpha]^{25}_D$ (*c* 1.4, $CHCl_3$): 102.9.

Heptamer (OAc, COOH), 13. Heptamer **12** (0.270 g, 0.087 mmol) was hydrogenolyzed to yield 0.190 g (75%) of a white solid.

IR (film, cm^{-1}): 3440(b), 2960, 2880, 1740, 1640, 1450, 1380, 1250, 1180, 1100, 1030, 760.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.08 (s, 7 H), 4.70 (m, 7 H), 2.28 (m), 2.114, 2.108, 2.03 (singlets, OAc protons), 1.80−0.94 (m), 0.91−0.73 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.56, 173.44, 173.32, 170.62, 170.55, 77.72, 77.69, 77.64, 77.21, 77.16, 76.85, 76.82, 75.96, 75.91, 75.87, 75.82, 75.66, 74.18, 73.93, 49.56, 49.51, 49.40, 47.85, 47.79, 47.74, 45.09, 45.02, 41.79, 41.72, 35.67, 34.86, 34.77, 34.70, 34.64, 34.61, 34.55, 34.44, 34.38, 34.18, 34.12, 34.02, 32.31, 32.24, 31.76, 31.62, 31.56, 31.53, 31.10, 31.07, 31.04, 30.98, 30.90, 30.86, 30.76, 27.50, 27.42, 27.37, 27.31, 26.86, 26.75, 26.61, 25.87, 25.78, 25.63, 23.46, 23.05, 21.43, 21.38, 17.59, 17.50, 17.47, 12.53, 12.44.

MALDI-TOF MS: 3000.7 (M + Na^+ 2999.2), 3017.1 (M + K^+ 3015.3).

Anal. Calcd for $C_{184}H_{284}O_{30}$: C, 74.26; H, 9.62. Found: C, 73.83; H, 9.67.

$[\alpha]^{25}_D$ (*c* 0.87, $CHCl_3$): 96.6.

Decamer (OAc, $COOCH_2$Np), 8. In an analogous manner, **11** (0.533 g, 0.406 mmol) and **7** (0.048 g, 0.088 mmol) yielded 280 mg (72%) of the title compound.

FT IR (film, cm^{-1}): 3357, 2945, 2869, 1733, 1513, 1450, 1379, 1246, 1172, 1093, 1027, 972, 756, 666.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.98 (d, 1 H, J = 7.5 Hz), 7.88−7.82 (m, 2 H), 7.56−7.43 (m, 4 H), 5.55 (s, 2 H), 5.07 (s, 10 H), 4.89 (s, 1 H), 4.68 and 4.53 (m, 10 H), 2.29 (m), 2.17 (m), 2.09, 2.08, 2.02 (singlets, OAc protons), 1.82−0.95 (m), 0.89−0.62 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.73, 173.55, 173.44, 173.26, 170.53, 170.39, 170.29, 133.69, 131.56, 131.46, 129.26, 128.71, 127.46, 126.50, 125.92, 125.23, 123.45, 77.21, 75.85, 75.78, 75.53, 74.15, 73.89, 64.39, 49.38, 48.05, 47.84, 47.72, 45.10, 45.06, 45.00, 41.77, 35.65, 34.77, 34.68, 34.59, 34.35, 33.99, 32.22, 31.72, 31.53, 31.20, 30.99, 30.82, 27.36, 26.85, 26.59, 25.85, 25.60, 23.45, 23.04, 22.54, 21.43, 21.34, 17.49, 12.53, 12.42, 12.11.

UV (THF, 22.8 μM), λ(log ϵ)): 292.2 (3.65), 281.3 (3.81), 271.6 (3.74), 226.3 (4.68).

HPLC: t_R = 8.5 min (40% THF/MeOH, λ = 280).

MALDI-TOF MS: 4447.6 (M + Na^+ 4447.2) and 4463.2 (M + K^+ 4463.4).

Anal. Calcd for $C_{275}H_{414}O_{44}$: C, 74.66; H, 9.43. Found: C, 74.31; H, 9.53.

$[\alpha]^{25}_D$ (*c* 1.67, $CHCl_3$): 103.6.

Decamer (OAc, COOH), 9. Hydrogenolysis of **8** (258 mg, 0.058 mmol) yielded 124 mg (50%) of the title compound.

FT IR (film, cm^{-1}): 3354, 2944, 2869, 1733, 1516, 1452, 1375, 1245, 1157, 1028, 755.

^{1} ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.08 (s,10 H), 4.90 (s, 1 H), 4.68 and 4.54 (m, 10 H), 2.28 (m), 2.17 (m), 2.09, 2.08, 2.02 (singlets, OAc protons), 1.94−0.96 (m), 0.89−0.71 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.54, 173.41, 173.33, 173.31, 173.29, 170.54, 170.47, 170.41, 170.39, 170.35, 170.28, 77.21, 77.12, 76.81, 76.44, 75.94, 75.84, 75.78, 75.58, 75.55, 74.14, 73.89, 73.83, 49.52, 49.45, 49.36, 47.83, 47.71, 45.09, 45.03, 44.98, 41.82, 41.75, 35.64, 34.85, 34.76, 34.66, 34.57, 34.34, 33.98, 32.31, 32.20, 32.11, 31.99, 31.72, 31.66, 31.57, 31.50, 31.03, 30.97, 30.93, 30.87, 30.81, 30.67, 27.43, 27.35, 27.27, 27.18, 26.94, 26.83, 26.57, 25.84, 25.60, 25.48, 23.43, 23.03, 21.42, 21.36, 21.34, 17.58, 17.47, 12.51, 12.40.

MALDI-TOF MS: 4321.6 (M + K^+ 4323.3).

$[\alpha]^{25}_D$ (*c* 1.23, $CHCl_3$): 98.4.

Tetramer (OAc, $COOCH_2$Np), 14. Starting with **6** (2.32 g, 4.339 mmol) and **7** (0.412 g, 0.75 mmol), 0.602 g (69%) of a white solid was obtained.

IR (film, cm^{-1}): 2960, 2880, 1730, 1470, 1440, 1380, 1360, 1250, 1180, 1030, 760.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.00 (d, 1 H, J = 7.5 Hz), 7.90−7.84 (m, 2 H), 7.55−7.43 (m, 4 H), 5.57 (s, 2 H), 5.09, 5.04 (s, s, 4 H), 4.90 (s, 4 H), 4.58 (s, 4 H), 2.28 (m), 2.20 (m), 2.133, 2.088, 2.081, 2.052 (singlets, OAc protons), 1.93−1.07 (m), 0.91−0.63 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.71, 173.39, 173.31, 173.13, 170.45, 170.37, 170.33, 170.23, 133.62, 131.51, 131.41, 129.20, 128.63, 127.47, 126.46, 125.87, 125.19, 123.44, 75.27, 75.22, 78.98, 70.57, 64.36, 47.70, 47.63, 47.40, 45.00, 44.98, 43.28, 40.81, 37.62, 34.59, 34.49, 34.45, 34.23, 31.62, 31.34, 31.13, 30.74, 30.66, 30.51, 28.77, 27.09, 26.80, 25.48, 22.72, 22.46, 21.54, 21.41, 21.36, 17.45, 17.39, 17.32, 12.17, 12.04.

UV (THF, 64.3 μM), λ(log ϵ)): 292.4 (3.69), 281.4 (3.86), 271.6 (3.78), 227.6 (4.44).

HPLC: t_R = 13.8 min (MeOH, λ = 280 nm).

MALDI-TOF MS: 2119.4 (M + Na^+ 2121.8), 2135.9 (M + K^+ 2137.9).

Anal. Calcd for $C_{125}H_{180}O_{26}$: C, 71.54; H, 8.64. Found: C, 71.83; H, 9.01.

$[\alpha]^{25}_D$ (*c* 2.66, $CHCl_3$): 80.8.

Tetramer (OAc, COOH), 15. Tetramer **14** was hydrogenolyzed to yield 0.400 g (86%) of a white solid.

IR (film, cm^{-1}): 3400 (b), 2960, 2880, 1730, 1440, 1370, 1240, 1020, 750.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.10, 5.09 (s, s, 4 H), 4.91 (s, 4 H), 4.58 (m, 4 H), 2.32 (m, 4 H), 2.24 (m, 4 H), 2.15, 2.13, 2.093, 2.086, 2.05 (singlets, OAc protons), 2.00−1.07 (m), 0.92−0.73 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.43, 173.31, 173.08, 170.52, 170.47, 170.39, 170.30, 77.20, 75.30, 75.18, 74.21, 74.03, 70.77, 70.63, 70.51, 47.81, 47.68, 47.54, 47.31, 45.06, 45.02, 43.31, 40.85, 37.68, 35.13, 34.96, 34.63, 34.55, 34.46, 34.33, 34.28, 31.96, 31.77, 31.49, 31.41, 31.18, 30.84, 30.78, 30.57, 28.82, 27.13, 27.07, 26.84, 25.54, 22.78, 22.50, 21.58, 21.44, 21.39, 17.55, 17.44, 17.39, 17.32, 12.22, 12.16.

MALDI-TOF MS: 1982.1 (M + Na^+ 1981.6), 1999.6 (M + K^+ 1997.7).

Anal. Calcd for $C_{114}H_{172}O_{26}$: C, 69.91; H, 8.85. Found: C, 69.69; H, 9.13.

$[\alpha]^{25}_D$ (*c* 1.55, $CHCl_3$): 80.6.

Nonamer (OAc, $COOCH_2Np$), 16. From **15** (0.357 g, 0.182 mmol) and **5** (0.035 g, 0.065 mmol) was obtained 0.0998 g (35%) of the title compound.

IR (film, cm^{-1}): 2950, 2900, 1740, 1250, 1040, 760.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.01 (d, 1 H, J = 9.6 Hz), 7.91−7.85 (m, 2 H), 7.61−7.43 (m, 4 H), 5.57 (s, 2 H), 5.09, 5.04 (s, s, 9 H), 4.90 (s, 8 H), 4.57 (m, 9 H), 2.27 (m), 2.147. 2.141, 2.132, 2.127, 2.09, 2.08, 2.05 (singlets, OAc protons), 2.00−1.07 (m), 0.94−0.63 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.79, 173.42,173.32, 173.11, 170.48, 170.45, 170.34, 170.25, 133.69, 131.58, 131.52, 129.21, 128.68, 127.44, 126.48, 125.91, 125.24, 123.51, 77.20, 75.32, 75.27, 74.02, 70.63, 64.38, 47.95, 47.79, 47.74, 47.44, 45.13, 45.07, 45.06,45.02, 43.34, 40.89, 37.72, 35.03, 34.66, 34.58, 34.35, 34.31, 34.03, 32.37, 31.92, 31.65, 31.43, 31.20, 30.82, 30.55, 28.84, 27.15, 26.86, 25.56, 23.08, 22.84, 22.52, 21.59, 21.44, 21.42, 21.39, 17.58, 17.53, 17.44, 17.35, 12.34.

UV (THF, 90.6 μM), λ(log ϵ)): 292.2 (3.68), 281.4 (3.85), 271.5 (3.79), 229.1 (4.30).

HPLC: t_R = 12.9 min (15% THF/MeOH, λ = 280).

MALDI-TOF MS: 4440.6 (M + Na^+ 4436.9).

Anal. Calcd for $C_{263}H_{388}O_{54}$: C, 71.57; H, 8.86. Found: C, 71.90; H, 9.26.

$[\alpha]^{25}_D$ (*c* 0.82, $CHCl_3$): 84.2.

Nonamer (OAc, COOH), 17. Nonamer **16** (108 mg, 0.024 mmol) was hydrogenolyzed to give 49 mg (47%)of the title compound.

IR (film, cm^{-1}): 3356, 2945, 1733, 1541, 1454, 1375, 1245, 1125, 1067, 1026, 755.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.08 (s, 9 H), 4.90 (s, 8 H), 4.57 (m, 9 H), 2.31−2.19 (m), 2.14, 2.13, 2.08, 2.04 (singlets, OAc protons), 1.99−1.06 (m), 0.91−0.72 (angular methyl groups).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.45, 173.39, 170.52, 170.40, 170.34, 170.30, 77.72, 77.63, 77.59, 77.20, 76.89, 76.81, 76.42, 75.64, 75.46, 75.33, 75.29, 75.20, 74.05, 73.93, 70.68, 70.59, 70.51, 47.85, 47.79, 47.71, 47.60, 47.57, 47.47, 47.45, 45.20, 45.07, 43.34, 40.89, 37.71, 34.99, 34.91, 34.87, 34.84, 34.66, 34.58, 34.35, 34.31, 31.56, 31.48, 31.43, 31.32, 31.21, 30.82, 30.77, 30.74, 30.65, 30.60, 30.55, 28.94, 28.84, 27.25, 27.16, 27.10, 27.00, 26.86, 25.56, 23.08, 22.81, 22.53, 21.59, 21.45, 21.41, 17.58, 17.53, 17.46, 17.40, 17.35, 12.35, 12.25.

MALDI-TOF MS: 4325.5 (M + K^+ 4312.9).

$[\alpha]^{25}_D$ (*c* 0.81, $CHCl_3$): 88.9.

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